U.S. FOOD & DRUG ADMINISTRATION

Human Foods Program

Amy Mozingo
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GRAS Associates, LLC
11810 Grand Park Avenue
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North Bethesda, MD 20852

Re: GRAS Notice No. GRN 001282

Dear Ms. Mozingo:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001282. We received the notice that you submitted on behalf of Zhucheng Haotian Pharm Co., Ltd. (ZCHT) on May 27, 2025, and filed it on August 18, 2025. ZCHT submitted an amendment to the notice on December 9, 2025 that provided additional information about production strains and updated literature search.

The subject of the notice is rebaudioside M produced by enzymatic treatment of rebaudioside A from the leaves of *Stevia rebaudiana* (Bertoni) Bertoni (rebaudioside M) for use as a general-purpose sweetener in foods, excluding infant formula and products under the U.S. Department of Agriculture's jurisdiction, at levels determined by good manufacturing practices. The notice informs us of ZCHT's view that these uses of rebaudioside M are GRAS through scientific procedures.

The rebaudioside M that is the subject of GRN 001282 is made from highly purified components of the leaves of the stevia plant. We note that a GRAS notice for the use of specific purified components of stevia, such as rebaudioside M, and FDA's response do not necessarily apply to the uses of other stevia products.

Our use of the terms "rebaudioside M," "steviol glycosides," or "SGs" in this letter is not our recommendation of these terms as appropriate common or usual names for declaring the substance in accordance with FDA's labeling requirements. Under 21 CFR 101.4, each ingredient must be declared by its common or usual name. In addition, 21 CFR 102.5 outlines general principles to use when establishing common or usual names for nonstandardized foods. Issues associated with labeling and the common or usual name of a food ingredient are under the purview of the Office of Nutrition and Food Labeling (ONFL) in the Nutrition Center of Excellence. The Office of Pre-Market Additive Safety did not consult with ONFL regarding the appropriate common or usual names for "rebaudioside M, "steviol glycosides," and "SGs."

ZCHT provides information about the identity and composition of rebaudioside M. ZCHT states that the subject of the notice is ≥95% total steviol glycosides (SGs) and ≥95% rebaudioside M and minor amounts of other SGs. Rebaudioside M (CAS No. 1220616-44-3) is a glycoside of steviol and is one of a group of known SGs, which differ from each other by the number of glycoside moieties and bonding order.

ZCHT describes the method of manufacture for rebaudioside M. ZCHT states that rebaudioside M is obtained through the enzymatic conversion of rebaudioside A from an extract of *S. rebaudiana* leaves. The enzymes include uridine diphosphate (UDP)-glucosyltransferases and a sucrose synthase that are obtained from fermentation of non-pathogenic and non-toxicogenic production microorganisms (*Escherichia coli* HT-UGT1, HT-UGT2, and HT-SUS). The three production strains are derived from *E. coli* K-12 MG1655 which has a history of safe use as a production source for food ingredients. ZCHT provides information on the parent strain and describes the construction of the production strains that includes gene deletions and insertion of synthesized genes. ZCHT states the production microorganisms do not contain any antimicrobial resistance genes and do not generate undesirable secondary metabolites during fermentation. ZCHT also confirms that the microbial DNA is undetectable in the final ingredient.

ZCHT states that the enzyme preparation is manufactured through the fermentation process under sterile and controlled conditions. The production organisms are grown in a culture medium and after the fermentation step is complete, the microbial biomass is separated from the media by centrifugation. The biomass is then resuspended in phosphate solution that is homogenized to extract the expressed enzymes. The mixture is centrifuged to remove cell debris, and the liquid retained for the enzymatic treatment of an *S. rebaudiana* extract. The extract is prepared from dried *S. rebaudiana* leaves that are extracted in hot deionized water and filtered to remove solid material. The aqueous extract is combined with ferrous sulfate and calcium oxide and the resulting mixture filtered to remove impurities such as proteins and polysaccharides. The resulting solution is deionized by the ion exchange resin and then treated with a macroporous resin onto which SGs are adsorbed. The resin is washed with deionized water, and ethanol is used to elute the SGs. Ethanol is removed and the solution is concentrated by heating and then spray-dried. The resulting powder is dissolved in an aqueous solution of ethanol and crystallized. The crystals are separated from the supernatant by centrifugation, dried, crushed, and screened to obtain the *S. rebaudiana* extract used as the starting material in the production of rebaudioside M. The *S. rebaudiana* extract and the enzymes are combined with sucrose and UDP sodium salt dissolved in phosphate solution. The reaction takes place under controlled conditions, and the resulting solution is heated to inactivate the enzymes. Diatomite is added to the solution that is then filtered to remove impurities. The solution is then collected in a tank for crystallization, and the crystals then separated by filtration. The crystals are dissolved in aqueous ethanol, and then re-crystallized. The product is centrifuged to obtain the secondary crystallization wet product that is then dried in an oven, crushed and sieved to obtain the final rebaudioside M product.

ZCHT provides specifications for rebaudioside M that include the content of total SGs (≥ 95 %, dry matter basis (DM)), rebaudioside M (≥ 95 % DM), limits for ash (≤ 1 %), loss on drying (≤ 5 %), lead (≤ 0.1 mg/kg), arsenic (≤ 0.1 mg/kg), cadmium (≤ 0.1 mg/kg), mercury (≤ 0.1 mg/kg), methanol (≤ 0.02 %), ethanol (≤ 0.3 %), and limits on microorganisms. ZCHT provides results from the analyses of five non-consecutive batches to demonstrate that rebaudioside M can be produced in accordance with the stated specifications. ZCHT provides the results of stability studies conducted with rebaudioside M and concludes that the shelf life of rebaudioside M is up to 3 years.

ZCHT provides estimates of dietary exposure to rebaudioside M. ZCHT discusses a published study on dietary exposures to rebaudioside A (Ref. 1). Based on the methodology described in Ref. 1 and a relative sweetness intensity as low as 200 times that of sucrose, ZCHT estimates the maximum dietary exposure in adults (expressed as steviol equivalents) to be 1.12 mg/kg body weight (bw)/day (d) and in children to be 1.24 mg/kg bw/d. ZCHT states that the use of rebaudioside M in food is self-limiting due to organoleptic factors and consumer taste considerations.

ZCHT summarizes published studies pertaining to the metabolic fate and safety of rebaudioside M. Based on pharmacokinetic studies, ZCHT concludes that microbes in the colon hydrolyze SGs completely to steviol and thus rebaudioside M shares a common metabolic fate. ZCHT discusses previously reviewed published acute, subchronic, and chronic toxicity/carcinogenicity studies, published multi-generational reproductive and developmental toxicology studies conducted with rebaudioside A, and *in vitro* and *in vivo* mutagenicity/genotoxicity studies for the safety conclusion for rebaudioside M. ZCHT includes an update of the literature regarding the safety of SGs through November 2025, and reports that no studies relevant to toxicology were found that would alter its safety conclusion.

To further support its view that rebaudioside M is GRAS for the intended use, ZCHT summarizes the decisions on the safety of SGs by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), the European Food Safety Authority, Food Standards Australia New Zealand, and Health Canada for use in food as sweeteners. ZCHT notes that JECFA has established an acceptable daily intake (ADI) for SGs of 0-4 mg/kg bw/d (expressed as steviol equivalents). This ADI was based on a no observed adverse effect level of 970 mg/kg bw/d (383 mg/kg bw/d, as steviol equivalents) from a two-year rat study, and the application of a safety factor of 100 to account for intra- and inter-species differences.

Based on all the available scientific information, ZCHT concludes that rebaudioside M is GRAS for its intended use in foods.

Standards of Identity

In the notice, ZCHT states its intention to use rebaudioside M in several food categories, including foods for which standards of identity exist, located in Title 21 of the CFR. We note that an ingredient that is lawfully added to food products may be used in a standardized food only if it is permitted by the applicable standard of identity.

Section 301(ll) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)

Section 301(ll) of the FD&C Act prohibits the introduction or delivery for introduction into interstate commerce of any food that contains a drug approved under section 505 of the FD&C Act, a biological product licensed under section 351 of the Public Health Service Act, or a drug or a biological product for which substantial clinical investigations have been instituted and their existence made public, unless one of the exemptions in section 301(ll)(1)-(4) applies. In our evaluation of ZCHT's notice concluding that rebaudioside M is GRAS under its intended conditions of use, we did not consider whether section 301(ll) or any of its exemptions apply to foods containing rebaudioside M. Accordingly, our response should not be construed to be a statement that foods containing rebaudioside M, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that ZCHT provided, as well as other information available to FDA, we have no questions at this time regarding ZCHT's conclusion that rebaudioside M is GRAS under its intended conditions of use. This letter is not an affirmation that rebaudioside M is GRAS under 21 CFR 170.35. Unless noted above, our review did not address other provisions of the FD&C Act. Food ingredient manufacturers and food producers are responsible for ensuring that marketed products are safe and compliant with all applicable legal and regulatory requirements.

In accordance with 21 CFR 170.275(b)(2), the text of this letter responding to GRN 001282 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2026.01.12 17:02:10 -05'00'

Susan J. Carlson, Ph.D.
Director
Division of Food Ingredients
Office of Pre-Market Additive Safety
Office of Food Chemical Safety, Dietary Supplements, and Innovation
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Reference

1. Renwick, A.G. 2008. The use of a sweetener substitution method to predict dietary exposures for the intense sweetener rebaudioside A. Food and Chemical Toxicology 46:S61–S69.